PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Michael Eppihimer, et al.	)	Group Art Unit: 1644
	)	
Serial No.: 09/825,580	)	Examiner: GAMBEL, P.
	)	
Filed: April 2, 2001	)	Confirmation No.: 9952
	)	
For: INHIBITION OF THROMBOSIS BY TREATMENT WITH P-SELECTIN ANTAGONISTS	)	

Attention: Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

REVISED APPEAL BRIEF UNDER BOARD RULE § 41.37

This paper is being filed in response to a Notice of Non-compliant Amendment mailed June 6, 2007. This Appeal Brief has been revised on page 7 to state the claims under appeal. A table illustrating representative support for the dependent claims has been added to pages 11 and 12. This Appeal Brief has also been revised in view of the Supreme Court's decision in *KSR Int'l Co. v. TeleFlex Inc.*, 127 S.Ct. 1727, (2007).

In support of the Notice of Appeal filed December 28, 2006, and further to Board Rule 41.37, Appellant presents this brief. A check for the fee of $500.00 required under 37 C.F.R. § 1.17(c) was submitted with the Appeal Brief filed on April 27, 2007.

This Appeal responds to the September 28, 2006, rejection of Claims 1-20, 25-27, 31-40, and 45, and 50-57, which are set forth in the attached Appendix.

If any additional fees are required or if the enclosed payment is insufficient, Appellant requests that the required fees be charged to Deposit Account No. 06-0916.

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I. Real Party In Interest

Genetics Institute, L.L.C. is assignee of record as evidenced by the assignment recorded on March 29, 2002, at reel 12772, frame 631, and as such, is the real party in interest in this appeal. Genetics Institute, L.L.C. is a subsidiary of Wyeth.

II. Related Appeals and Interferences

There are currently no other appeals or interferences, of which appellant, appellant's legal representative, or assignee are aware, that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. Status Of Claims

Claims 1-20, 25-27, 31-40, and 45, and 50-57 are pending in this application and are currently rejected. Claims 21-24, 28, 41, and 42 are cancelled, while claims 29, 30, 43, 44, and 46-49 are withdrawn. The claims are provided in an Appendix to the appeal brief. As argued below, Appellants believe that the rejected claims are patentable.

Appellants appeal the rejection of claims 1-20, 25-27, 31-40, and 45, and 50-57.

IV. Status Of Amendments

The most recent amendments were made on September 13, 2006. Therefore, all amendments to the specification and claims have been entered, and no amendments have been made subsequent to the September 13, 2006, Response.

V. Summary Of Claimed Subject Matter

The present invention relates to methods of treating thromboses in a subject having hypertension. In particular, the method involves providing a patient a P-selectin ligand glycoprotein ligand 1 (PSGL-1). PSGL-1 is a high affinity ligand for P-selectin, and it may also bind to E-selectin and L-selectin. *Specification*, page 2, lines 6-7. PSGL-1 is expressed by leukocytes and mediates cell adhesion between leukocytes, platelets and endothelial cells. *Id.* at 8-9. Cell adhesion, in turn, plays a role in thrombosis, which is the formation of a blood clot or thrombus. *Id.* at 1, line 5. Thromboses may form following blood vessel injury by invasive procedures such as angioplasty or coronary bypass surgery, or may be caused by cardiovascular conditions. *Id.* at lines 23-32. Thrombosis is a serious medical condition that can cause tissue damage and, if untreated, death. *Id.* at 1, lines 18-19.

The present invention is based, in part, on the discovery that antagonists of P-selectin, including soluble PSGL-1 protein and PSGL fusion protein, inhibit cellular adhesion, thereby inhibiting formation of thrombosis. Thus, providing a patient with a PSGL-1 protein could treat or inhibit thrombus formation. The current claims focus on treatment of a subject having hypertension. While subjects with a variety of different conditions could be treated with the claimed method, Appellants selected "hypertension" at the request of the Examiner. *See* Interview Summary attached to Office Action mailed September 9, 2004.

Independent claim 1 focuses on a method of treating or inhibiting thrombosis in a subject suffering from hypertension. It recites a method comprising administering to a

subject having hypertension a composition comprising a PSGL-1 protein which has P-selectin ligand activity. The recited P-selectin ligand activities include a) inhibiting P-selectin or E-selectin binding; b) inhibiting adhesion of at least one of leukocytes to endothelial cells, leukocytes to platelets, leukocytes to blood vessels, and platelets to blood vessels; c) inhibiting leukocyte recruitment to platelets and endothelial cells; d) increasing leukocyte migration; e) increasing movement of at least one of leukocytes and platelets relative to blood vessels; and f) increasing leukocyte rolling velocity.

Independent claim 25 focuses on a method of inhibiting thrombus that is induced by a thrombus-inducing agent in a subject having hypertension. It recites a method comprising identifying a subject having hypertension and administering to the subject a composition comprising an effective amount of soluble PSGL-1 protein or a fragment thereof having a P-selectin ligand activity chosen from the same activities that are recited in independent claim 1.

Independent claim 31 is directed to a method of preventing deep vein thrombosis (DVT). DVT is the formation of thrombus within a deep vein. Specification, p. 1, lines 8-9. Claim 31 recites a method comprising identifying a subject having or at risk for DVT and administering to the subject a composition comprising an effective amount of a soluble PSGL-1 protein or a fragment thereof having a P-selectin ligand activity chosen from the same activities that are recited in independent claim 1.

Independent claim 45 focuses on a prophylactic method of treating or inhibiting thrombosis in a subject with hypertension. It recites a method comprising identifying a

subject at risk of thrombosis due to hypertension and administering to the subject a composition comprising an effective amount of a PSGL-1 protein or a fragment thereof having a P-selectin ligand activity chosen from the same activities that are recited in independent claim 1.

Independent claim 57 is directed to a method of treating, inhibiting or preventing thrombosis in a subject at risk for thrombosis. It recites a method comprising identifying a human subject at risk of thrombosis due to hypertension and administering to the subject a composition comprising an effective amount of a soluble PSGL-1 protein or fragment thereof having a P-selectin activity chosen from the same activities that are recited in independent claim 1.

The following table maps the support for the pending claims:

Claims	Representative Support in Application
1, 25, 31,45, and 57	page 2, lines 11-24 page 4, lines 33-37 page 6, lines 27-30 and lines 36-37 page 7, lines 2-37 page 31, lines 22-24 page 32, lines 2-11 Figures 2-5
2	page 2, lines 29-33
3, 32, and 50	page 2, lines 28-19
4	page 2, lines 29, 33
5	page 3, lines 6-8
6	page 3, lines 6-8
7	page 4, 19-22
8-13, 33-39, 51-53, and 56	page 2, line 37, to page 3, line 3.
14	page 2, lines 10-13
15 and 55	page 3, lines 6-8
16	page 2, line 37.
17	page 7, lines 12-14

Claims	Representative Support in Application
18-20	page 36, lines 17-21; and page 48, lines 20-22
26 and 54	page 12, lines 19-20
27	Page 56, lines 1-2; Figure 5
29 and 43	Page 1, lines 14-18
30, 44, and 46	page 6, line 37 to page 7, line 6
40	page 7, lines 7-11

VI. Grounds of Rejection

A. Claims 1-4, 8-13, 16-18, 25-27, 45-47, 50-53, and 57 stand rejected under 35 U.S.C. § 102(e).

B. Claims 1-20, 25-27, 31-40, 45, and 50-57 stand rejected under 35 U.S.C. § 103(a).

VII. Argument

A. The Subject Matter Of The Claims Is Not Present Literally Or Inherently In The Prior Art

In the Office Action mailed September 28, 2006, the Office rejects claims 1-4, 8-13, 16-18, 25-27, 45-47, and 50-53 under 35 U.S.C. § 102(e) as inherently anticipated by U.S. Patent No. 5,464,778 ("Cummings") as evidenced by THE MERCK MANUAL OF DIAGNOSIS AND THERAPY 1655 (17th ed. 1999) ("Merck Manual") and Lip *et al.*, "Hypertension and the prothrombotic state," J. Hum. Hyper. 14: 687-90 (2000) ("Lip"). Office Action, p. 3.

Appellants respectfully assert that claims 1-4, 8-13, 16-18, 25-27, 45-47, 50-53, and 57 are not anticipated because these claims recite subject matter that is not present literally or inherently in the prior art. In rejecting these claims, the Office relies on an improper standard for finding inherent anticipation. The prior art relied on by the Office does not disclose that hypertension is necessarily present in patients with thrombosis. Appellants also rely on a Declaration of Dr. Stefan Hemmerich on September 13, 2006. This Declaration is included in the attached Appendix.

1. A Finding Of Inherent Anticipation Requires That The Missing Descriptive Matter Is Necessarily Present In The Applied References

A claim is anticipated "only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP § 2131 (8th ed., 2d rev. 2004) (citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987)). Normally, only a single reference should be used in rejecting an application under 35 U.S.C. § 102, though a § 102 rejection over multiple

references has been found proper where the additional reference was cited: (1) to prove the primary reference contains an enabled disclosure; (2) to explain the meaning of a term used in the primary reference; or (3) to show that a characteristic not disclosed in the primary reference is inherent. MPEP § 2131.01. The reference "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference." MPEP § 2112 (citing *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1376 (Fed. Cir. 2003)) (emphasis added). Finally, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." MPEP § 2112 (citing *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999)). The burden is on the Office to "provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." MPEP § 2112 (citing *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)).

The recent Federal Circuit decision of *Perricone v. Medicis*, 432 F.3d 1368 (Fed. Cir. 2005), in which the court found lack of inherent anticipation, is instructive. In *Perricone*, the court considered whether a claim to a method of treating sunburn using a particular formulation was inherently anticipated by a prior patent that disclosed a similar formulation for use on skin. As stated by the court, "[i]f Pereira [the prior art] discloses the very same methods, then the particular benefits must naturally flow from those methods, even if not recognized as benefits at the time of Pereira's disclosure." *Perricone* F.3d at 1378 (emphasis added). In finding that the claimed method was not

inherently anticipated, the court stated "[t]he issue is not, as the dissent and the district court imply, whether Pereira's lotion would inherently treat that damage, but whether Pereira discloses the application of its composition to skin sunburn." *Id.* at 1378. The court concluded "[i]t does not," and that the claimed method of treating sunburn "recites a new use of the composition disclosed by Pereira, the treatment of sunburn." *Id.* at 1337-79. Thus, the Federal Circuit clearly indicates that the mere possibility that a compound disclosed in the prior art could function in a particular manner does not preclude the patenting of a new use for the compound.

The Federal Circuit's decision in *Schering Corp. v. Geneva Pharmaceuticals, Inc.,* 339 F.3d 1373, 1376 (Fed. Cir. 2003) demonstrates the close relationship that must exist between the prior art and the later claimed invention for a finding of inherent anticipation. In *Schering*, the plaintiff obtained a patent that claimed the antihistamine loratadine, and obtained a later patent that claimed a metabolite of loratadine, DCL. The district court granted summary judgment to defendants who argued that the disclosure of loratadine inherently anticipated its metabolite, DCL. *Schering*, 339 F.3d at 1374. The Federal Circuit affirmed the lower court's ruling. *Id.* at 1382. The Federal Circuit noted that the metabolite was not expressly disclosed in the antihistamine patent, but that "the record demonstrated that DCL necessarily and inevitably forms from loratadine under normal conditions. DCL is a necessary consequence of administering loratadine to patients". *Id.* at 1378 (emphasis added). Accordingly, a loose association between the disclosure of the alleged anticipatory reference and the

later claimed subject matter is not sufficient to find anticipation. Rather, there must be a necessary relationship between the two.

2. Hypertension Is Not Necessarily Associated With The Conditions Of Cummings

In rejecting claims 1-4, 8-13, 16-18, 25-27, 45-47, 50-53, and 57, the Office fails to meet its burden in showing that hypertension is necessarily associated with the conditions of Cummings. The Office does not argue that the claimed invention is explicitly disclosed in the prior art, but cites The Merck Manual and Lip to show that hypertension is inherent in the conditions of Cummings. Office Action, p. 3. Cummings discusses the treatment of several conditions including atherosclerosis, stroke, and conditions produced by ischemia/reperfusion injury. *See* col. 18, line 54 to col. 19, line 20, and col. 19, line 64 to col. 20, line 5. Cummings does not teach that these conditions are associated with hypertension.

The reliance on The Merck Manual by the Office is misplaced because The Merck Manual actually exemplifies the distinct nature of hypertension and the conditions of Cummings. For example, the Merck Manual describes the characteristics of atherosclerotic vessels and then describes the distinct characteristics of such vessels when hypertension is present. THE MERCK MANUAL OF DIAGNOSIS AND THERAPY 1655 (17th ed. 1999). This description indicates that hypertension and atherosclerosis need not coexist. In fact, hypertension is not listed as a symptom characteristic of atherosclerosis in the passage of the Merck Manual cited by the Office, which states that "[a]therosclerosis is characteristically silent until critical stenosis,

thrombosis, aneurysm, or embolus supervenes." THE MERCK MANUAL OF DIAGNOSIS AND THERAPY 1657 (17th ed. 1999).

Moreover, the Office cites passages of the Merck Manual that describe hypertension as a "risk factor" for several diseases. Office Action, p. 3. For example, the Office quotes the Merck Manual's statement that hypertension is one of "three risk factors, along with cigarette smoking and hypercholesterolemia predisposing to coronary atherosclerosis" and hypertension is the "most important risk factor predisposing to stroke." *Id.* The Merck Manual's treatment of hypertension as one of several "risk factors" highlights how certain conditions may alter the probability or possibility of a particular disease but that such factors are not necessarily associated with the disease. A risk factor may be more "important" than others, suggesting a stronger association between the disease and the risk factor. Nevertheless, the risk factor indicates a probability or possibility of association, not a necessary association.

Lip also fails to demonstrate that hypertension is necessarily associated with the conditions of Cummings. Similar to The Merck Manual, Lip describes the association as one of risk, not certainty. Lip describes haemostatic abnormalities that "appear to be additive to conventional risk factors for cardiovascular and cerebrovascular events." Lip, p. 687 (emphasis added). If fact, far from teaching a necessary association between hypertension and the conditions of Cummings, Lip discusses the uncertain relationship between the two. Lip speculates that, "[s]ince the processes of thrombogenesis and atherogenesis have certain similarities to inflammatory disease, the elevations in various indices may reflect the severity of vascular disorders as a secondary phenomenon rather than act as a true prognostic factor." *Id.* at 689. Thus,

Lip makes clear that there is not a necessary association between hypertension and cardiovascular conditions, and Lip further indicates that there was uncertainty about the significance of any correlation between these phenomena when the invention was made. Accordingly, The Merck Manual and Lip do not support the contention that hypertension is necessarily associated with the conditions of Cummings, and Cummings does not inherently anticipate the claimed method.

3. It Is Known To Those Of Ordinary Skill In The Art That Hypertension Is Not Necessarily Present In The Conditions Of Cummings

The Merck Manual indicates that there may be a correlation between hypertension and various conditions, but hypertension is just one of many risk factors that might predispose a patient to certain conditions. It is well known by those skilled in the art that patients with atherosclerosis need not also have hypertension. *See* Hemmerich Declaration, paragraph 7(A).

The Merck Manual teaches that strokes can be caused by arteriosclerotic or hypertensive stenosis, thrombosis or embolism. (*See* page 1421). The Merck Manual does not teach that stroke is necessarily associated with hypertension. In totality, the Merck Manual indicates that hypertension and stroke do not always coexist and patients suffering from a stroke do not always have hypertension. This is well known among those skilled in the art. *See* Hemmerich Declaration, paragraph 7(B).

The Merck Manual teaches that a number of factors including hypertension predispose a patient to Transient Ischemic Attacks (TIA). However, it is known to those

of skill in the art that ischemia and hypertension need not always coexist. *See* Hemmerich Declaration, paragraph 7(C).

The Office has not shown inherent anticipation by Cummings. Cummings does not teach that hypertension is necessarily associated with the conditions of Cummings, and neither The Merck Manual not Lip show that hypertension is necessarily present in the diseases of Cummings. Moreover, those of skill in the art recognize that hypertension is not necessarily present in the diseases in Cummings. *See* Hemmerich Declaration. Accordingly, the instantly claimed invention is not inherently anticipated, and Appellants respectfully request that the rejection of claims 1-4, 8-13, 16-18, 25-27, 45-47, 50-53, and 57 be withdrawn.

B. The Subject Matter Of The Claims Is Not Obvious

The Office maintains the prior rejection of claims 1-20, 25-27, 31-40, 45, and 50-57 under 35 U.S.C.§ 103(a) as allegedly unpatentable over Cummings and Larsen *et al.*, U.S. Patent No. 5,840,679 ("Larsen") in view of Blann *et al.*, "Evidence of platelet activation in hypertension," J. Hum. Hyper. 11:607-609 (1997) ("Blann"), Araneo *et al.*, U.S. Patent No. 6,150,348 ("Araneo") and DeFrees *et al.*, U.S. Patent No. 5,604,207 ("DeFrees"), and further in view of the Merck Manual. Office Action, p. 5. The Office apparently contends that administration of PSGL-1 to treat the conditions recited in Cummings and Larsen would inherently treat hypertension, and therefore thrombosis. *Id.*

Appellants respectfully assert that the claimed invention is not obvious in view of the publications cited by the Office. Hypertension and thromboses need not coexist.

Accordingly, the skilled artisan would not know if a patient suffering from hypertension also suffered from thromboses, and it would not be obvious to treat such a subject with PSGL-1. A described in detail below, none of the publications relied upon by the Office supply the necessary link between hypertension, thromboses, and treatment with PSGL-1. As such, these publications, whether considered alone or together, fail to make out a *prima facie* case of obviousness.

The Examiner bears the burden of establishing *prima facie* obviousness. *See* M.P.E.P. § 2142. To establish obviousness "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does." *KSR Int'l Co. v. TeleFlex Inc.*, 127 S.Ct. 1727, 1741 (2007). A reason to combine is important because "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* On the contrary, "demonstrating a teaching, suggestion, or motivation to combine known elements in order to show the combination is obvious . . . captures a helpful insight." *Id.*

Applicants respectfully assert that the Office has not demonstrated *prima facie* obviousness because the Office has failed to provide a reason that would have prompted a person of ordinary skill in the art to combine reference teaches to arrive at the claimed invention.

1. The Office Provides No Reason to Combine References

In rejecting the claimed methods as obvious, the Office relies upon an improper finding of inherency, and thus a reason to combine references is lacking. Cummings

and Larsen neither teach nor suggest the use of a PSGL-1 protein for treating or inhibiting thrombosis in a patient with hypertension. As noted above, Cummings neither teaches nor suggests that hypertension is necessarily associated with any of the conditions discussed therein, and the lack of a necessary association between hypertension and the conditions of Cummings was known to those of skill in the art. *See* Hemmerich Declaration, paragraph 8. Larson, Blann, Araneo, Defrees and The Merck Manual also fail to show such a necessary association and does not provide a reason to arrive at the claimed invention.

a. Cummings

As noted above, Cummings discusses the treatment of several conditions including atherosclerosis, stroke, and conditions produced by ischemia/reperfusion injury. *See* col. 18, line 54 to col. 19, line 20, and col. 19 line 64 to col. 20, line 5. Cummings does not teach that these conditions are associated with hypertension.

b. Larsen

Larsen describes a P-selectin ligand protein, and methods of treating numerous conditions using P-selectin ligand (*See* column 15, lines 50-66). Larsen does not mention treatment of subjects with hypertension nor does Larsen teach that conditions that might be treated with P-selectin ligand are associated with hypertension. Larsen also fails to teach that a composition having P-selectin ligand activity could be used to treat or inhibit thrombosis, thrombus formation or deep vein thrombosis in a subject having hypertension. The disclosure in Larsen, whether alone or when combined with Cummings, would not suggest to the skilled artisan that a composition having P-selectin ligand activity could be used to treat or inhibit thrombosis, thrombus formation or deep

vein thrombosis in a subject having hypertension. *See* Hemmerich Declaration, paragraph 10.

c. Blann

Blann speculates that compounds that reduce platelet activity, such as aspirin, could be useful to treat thrombosis but does not teach that a composition having P-selectin ligand activity could be used to treat or inhibit thrombosis, thrombus formation, or deep vein thrombosis in a subject having hypertension. (Blann, page 608). There is no suggestion in Blann that PSGL-1 could be substituted for the compounds discussed in Blann, and Blann provides no reason to do so. Moreover, to one skilled in the art, the disclosure in Blann would not suggest that a composition having P-selectin ligand activity could be used to treat or inhibit thrombosis, thrombus formation or deep vein thrombosis in a subject having hypertension. *See* Hemmerich Declaration, paragraph 11.

d. Araneo

Araneo discusses methods of preventing or reducing the effects of ischemia and other conditions including pulmonary hypertension by administering the steroid DHEA, a very different compound from the instantly claimed protein. (*See* Abstract. *See also* column 4). Araneo does not teach or suggest that a composition having P-selectin ligand activity could be used to treat or inhibit thrombosis, thrombus formation, or deep vein thrombosis in a subject having hypertension, but suggests a treatment based on reducing the level of P-selectin expression. (*See* column 17, lines 59-64). Araneo does not teach or suggest methods of treatment of a subject suffering from hypertension with PSGL-1. To one skilled in the art, the disclosure in Blann would not suggest that a

composition having P-selectin ligand activity could be used to treat or inhibit thrombosis, thrombus formation or deep vein thrombosis in a subject having hypertension. *See* Hemmerich Declaration, paragraph 12.

e. DeFrees

DeFrees describes analogs of sialyl Le^X and speculates about the use of these compounds to treat inflammatory disorders, and mentions the use of these analogs to treat deep vein thrombosis. (*See* column 3 and column 44, lines 35-65; *see also* column 45, lines 7-15). However, DeFrees does not teach or suggest to the skilled artisan the treatment of deep vein thrombosis in a subject with hypertension. DeFrees fails to even mention hypertension. To the skilled artisan, DeFrees fails to suggest any relationship between P-selectin or PSGL-1 and the treatment of thrombosis in a subject with hypertension. *See* Hemmerich Declaration, paragraph 13.

f. The Merck Manual

As noted above, The Merck Manual merely describes a correlation between hypertension and certain conditions, but hypertension is just one of many risk factors that might predispose a patient to these conditions. Moreover, it is well known by the skilled artisan that patients with thrombotic conditions need not also have hypertension. *See* Hemmerich Declaration, paragraphs 7-8.

Because of the shortcomings of Blann, Araneo, DeFrees and the Merck Manual, these publications fail to cure the deficiencies of Cummings and Larsen. First, none of these references teach or suggest that hypertension is necessarily associated with the conditions discussed in Cummings and/or Larsen, and it would not be obvious to treat a patient suffering from a condition of Cummings and/or Larsen as the skilled artisan

would not know whether the patient had hypertension. Second, each of Blann (aspirin), Araneo (hormone), and DeFrees (analogues of sialyl-Lewis^x) discuss compounds other than a PSGL-1 protein. In the absence of a known or inherent association between hypertension and the conditions of Cummings or Larsen, and a teaching or suggestion to substitute PSGL-1 for the variety of compounds disclosed, one of skill in the art would have no reason to arrive at the claimed invention by combining references.

2. Claim 27 is Not *Prima Facie* Obvious

The Office maintains the prior rejection of claim 27 under 35 U.S.C.§ 103(a) as allegedly unpatentable over Cummings and Larsen, in view of Blann, Araneo, DeFrees, the Merck Manual, as applied to claims 1-20, 25-27, 31-40, 45, and 50-57 above, and further in view of Maugeri *et al.*, "Polymorphonuclear Leukocyte-Platelet Interaction: Role of P-selectin in Thromboxane B_2 and Leukotriene C_4 Cooperative Synthesis," *Thromb. Haem.* 72:450-456 (1994) ("Maugeri") and Johnston *et al.,* "Differential Roles of Selectins and the α4-Integrin in Acute, Subacute, and Chronic Leukocyte Recruitment In Vivo," *J. Immunol.* 159:4514-4523 (1997) ("Johnston"). Office Action, p. 10. The Office concedes that Cummings and Larsen do not disclose the role of LTC_4 in thrombus formation or thrombotic conditions *per se*, but maintains that LTC_4 was a known thrombus-inducing agent involved in thrombus formation and thrombotic conditions, as allegedly shown by Maugeri and Johnston. *Id.* at 11.

a. Maugeri

Maugeri investigates a relationship between LTC_4 and the aggregation of mixtures containing platelets and polymorphonuclear leukocytes, and describes

decreased aggregation of these mixtures in the presence of an anti-P-selectin antibody *in vitro*. (*See* Introduction and Figure 2). Maugeri does not mention the use of a P-selectin ligand protein to treat thrombosis, and does not mention any relationship between thrombosis formation and hypertension. To one of ordinary skill in the art, the disclosure of Maurgeri would not suggest a method of treating or inhibiting thrombus formation induced by a thrombus-inducing agent in a subject comprising identifying a subject having hypertension and administering to the subject a composition of a PSGL-1 protein, or said method wherein the thrombus inducing agent is LTC_4. *See* Hemmerich Declaration, paragraph 15.

b. Johnston

Johnston investigates the ability of anti-P-selectin antibodies to inhibit LTC_4-induced leukocyte rolling *in vitro* (*See, e.g.*, Figure 1). Johnston speculates about anti-inflammatory strategies designed to block leukocyte recruitment but does not identify the use of a P-selectin protein. (*See* page 4532). Moreover, Johnston fails to teach or suggest any relationship between thrombus formation and hypertension. To one of ordinary skill in the art, the disclosure of Johnston would not suggest a method of treating or inhibiting thrombus formation induced by a thrombus-inducing agent in a subject comprising identifying a subject having hypertension and administering to the subject a composition of a PSGL-1 protein, or said method wherein the thrombus inducing agent is LTC_4. *See* Hemmerich Declaration, paragraph 16.

As noted above, neither Larsen nor Cummings teach or suggest treating or inhibiting thrombosis in a subject with hypertension and Blann, Araneo, DeFrees or the Merck Manual do not compensate for this deficiency, since none of these documents

discuss administering a PSGL-1 protein for treating or inhibiting thrombosis in a subject having hypertension. Similarly, neither Maugeri nor Johnston compensate for these deficiencies because they also fail to discuss treating or preventing thrombosis in a subject having hypertension using a P-selectin ligand protein. To one of skill in the art, Maugeri and Johnston would not render the claimed invention obvious. *See* Hemmerich Declaration, paragraph 17.

Accordingly, Appellants respectfully request the withdrawal of the rejection of claim 27.

VIII. Conclusion

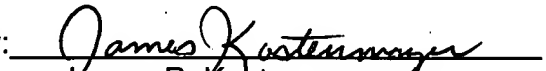
For the reasons given above, pending claims 1-20, 25-27, 31-40, and 45, and 50-57 are allowable and reversal of the Examiner's rejection is respectfully requested.

To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Appeal Brief, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: July 6, 2007

By: 
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IX. Claims Appendix to Appeal Brief Under Rule 41.37(c)(1)(viii)

1. (Previously presented) A method of treating or inhibiting thrombosis in a subject having hypertension comprising administering to the subject a composition comprising an effective amount of a PSGL-1 protein having a P-selectin ligand activity chosen from at least one of:

a) inhibiting P-selectin or E-selectin binding;

b) inhibiting adhesion of at least one of leukocytes to endothelial cells, leukocytes to platelets, leukocytes to blood vessels, and platelets to blood vessels;

c) inhibiting leukocyte recruitment to platelets and endothelial cells;

d) increasing leukocyte migration;

(e) increasing movement of at least one of leukocytes and platelets relative to blood vessels; and

f) increasing leukocyte rolling velocity.

2. (Previously presented) The method of claim 1, wherein the PSGL-1 protein is a soluble PSGL-1 protein or a fragment thereof having a P-selectin ligand activity.

3. (Original) The method of claim 2, wherein the soluble PSGL-1 protein is human PSGL-1.

4. (Original) The method of claim 2, wherein the soluble PSGL-1 protein is a recombinant protein.

5. (Original) The method of claim 2, wherein the soluble PSGL-1 protein comprises an Fc portion of an immunoglobulin.

6. (Original) The method of claim 5, wherein the immunoglobulin is human IgG1.

7. (Original) The method of claim 2, wherein the soluble PSGL-1 protein is a recombinant human PSGL-Ig fusion protein.

8. (Previously presented) The method of claim 2, wherein the soluble PSGL-1 protein comprises an extracellular domain of human PSGL-1 protein or a fragment thereof, capable of treating or inhibiting thrombosis.

9. (Original) The method of claim 8, wherein the fragment comprises the amino acid sequence set forth in SEQ ID NO:2 from amino acid 42 to amino acid 60.

10. (Original) The method of claim 8, wherein the fragment comprises the amino acid sequence set forth in SEQ ID NO:2 from amino acid 42 to amino acid 88.

11. (Original) The method of claim 8, wherein the fragment comprises the amino acid sequence set forth in SEQ ID NO:2 from amino acid 42 to amino acid 118.

12. (Original) The method of claim 8, wherein the fragment comprises the amino acid sequence set forth in SEQ ID NO:2 from amino acid 42 to amino acid 189.

13. (Original) The method of claim 8, wherein the fragment comprises the amino acid sequence set forth in SEQ ID NO:2 from amino acid 42 to amino acid 310.

14. (Original) The method of claim 2, wherein the soluble PSGL-1 protein comprises the amino acid sequence from amino acid 42 to amino acid 88 of SEQ ID NO:2 fused at its C-terminus to an Fc portion of an immunoglobulin.

15. (Original) The method of claim 8, wherein the soluble PSGL-1 protein further comprises an Fc portion of an immunoglobulin.

16. (Original) The method of claim 1, wherein the subject is human.

17. (Previously presented) The method of claim 1, wherein the PSGL-1 protein is administered to the subject prior to thrombus formation.

18. (Original) The method of claim 2, wherein the effective amount of soluble PSGL-1 protein or fragment thereof is between approximately 0.1 mg/kg and 10 mg/kg.

19. (Original) The method of claim 18, wherein the effective amount of soluble PSGL-1 protein is approximately 1 mg/kg.

20. (Previously presented) The method of claim 18, wherein the effective amount of soluble PSGL-1 protein is chosen from 0.1 mg/kg, 0.25 mg/kg, 0.5 mg/kg, 0.75 mg/kg, 1.0 mg/kg, 1.25 mg/kg, 1.5 mg/kg, 1.75 mg/kg, 2.0 mg/kg, 2.25 mg/kg, 2.5 mg/kg, 3.0 mg/kg, and 3.5 mg/kg.

21-24. (Canceled)

25. (Previously presented) A method for inhibiting thrombus formation induced by a thrombus-inducing agent in a subject comprising identifying a subject having hypertension and administering to the subject a composition comprising an effective amount of soluble PSGL-1 protein or a fragment thereof having a P-selectin ligand activity chosen from at least one of:

a) inhibiting P-selectin or E-selectin binding;

b) inhibiting adhesion of at least one of leukocytes to endothelial cells, leukocytes to platelets, leukocytes to blood vessels, and platelets to blood vessels;

c) inhibiting leukocyte recruitment to platelets and endothelial cells;

d) increasing leukocyte migration;

e) increasing movement of at least one of leukocytes and platelets relative to blood vessels; and

f) increasing leukocyte rolling velocity.

26. (Previously presented) The method of claim 25, wherein the soluble PSGL-1 protein or fragment thereof having a P-selectin ligand activity comprises a non-PSGL-1 amino acid sequence.

27. (Original) The method of claim 25, wherein the thrombus-inducing agent is LTC_4.

28. (Canceled)

29. (Withdrawn) The method of claim 1, wherein the subject has a condition chosen from prolonged sitting, bed rest and immobilization.

30. (Withdrawn) The method of claim 1, wherein the subject is at risk of thrombosis due to a vascular procedure chosen from angioplasty, surgical revascularization, balloon angioplasty, laser angioplasty, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, rotational atherectomy, stenting, and coronary artery stenting.

31. (Previously presented) A method of preventing or treating deep vein thrombosis, comprising identifying a subject having or at risk for deep vein thrombosis and administering to a subject a composition comprising an effective amount of a soluble PSGL-1 protein or a fragment thereof having a P-selectin ligand activity chosen from at least one of:

a) inhibiting P-selectin or E-selectin binding;

b) inhibiting adhesion of at least one of leukocytes to endothelial cells, leukocytes to platelets, leukocytes to blood vessels, and platelets to blood vessels;

c) inhibiting leukocyte recruitment to platelets and endothelial cells;

d) increasing leukocyte migration;

e) increasing movement of at least one of leukocytes and platelets relative to blood vessels; and

f) increasing leukocyte rolling velocity.

32. (Previously presented) The method of claim 31, wherein the soluble PSGL-1 protein or fragment thereof is a human PSGL-1.

33. (Previously presented) The method of claim 31, wherein the soluble PSGL-1 protein or fragment thereof comprises an extracellular domain of human PSGL-1 protein.

34. (Previously presented) The method of claim 31, wherein the soluble PSGL-1 protein or fragment thereof comprises amino acid 42 to amino acid 60 of SEQ ID NO:2.

35. (Previously presented) The method of claim 31, wherein the soluble PSGL-1 protein or fragment comprises the amino acid sequence set forth in SEQ ID NO:2 from amino acid 42 to amino acid 88.

36. (Previously presented) The method of claim 31, wherein the soluble PSGL-1 protein or fragment thereof comprises a non-PSGL-1 amino acid sequence.

37. (Previously presented) The method of claim 36, wherein the non-PSGL-1 amino acid sequence comprises an Fc portion of an immunoglobulin.

38. (Previously presented) The method of claim 37, wherein the soluble PSGL-1 protein or fragment comprises the amino acid sequence from amino acid 42 to amino acid 60 of SEQ ID NO:2.

39. (Previously presented) The method of claim 37, wherein the soluble PSGL-1 protein or fragment comprises the amino acid sequence from amino acid 42 to amino acid 88 of SEQ ID NO:2.

40. (Previously presented) The method of claim 31, wherein the subject is at risk for deep vein thrombosis due to hypertension.

41-42.(Canceled)

43. (Withdrawn) The method of claim 31, wherein the subject is at risk for deep vein thrombosis due to prolonged sitting, bed rest or immobilization.

44. (Withdrawn) The method of claim 31, wherein the subject is at risk for deep vein thrombosis due to a vascular procedure chosen from angioplasty, surgical revascularization, balloon angioplasty, laser angioplas ty, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, rotational atherectomy, stenting, and coronary artery stenting.

45. (Previously presented) A prophylactic method of treating or inhibiting thrombosis in a human subject comprising identifying a subject at risk of thrombosis due to hypertension and administering to the subject a composition comprising an effective amount of a PSGL-1 protein or a fragment thereof having a P-selectin ligand activity chosen from at least one of:

a) inhibiting P-selectin or E-selectin binding;

b) inhibiting adhesion of at least one of leukocytes to endothelial cells, leukocytes to platelets, leukocytes to blood vessels, and platelets to blood vessels;

c) inhibiting leukocyte recruitment to platelets and endothelial cells;

d) increasing leukocyte migration;

e) increasing movement of at least one of leukocytes and platelets relative to blood vessels; and

f) increasing leukocyte rolling velocity.

46. (Withdrawn) The method of claim 45, wherein the subject is at risk of thrombosis due to a disorder, condition or procedure chosen from:

(a) a cardiovascular disease or disorder;

(b) prolonged sitting, bed rest, or immobilization; and

(c) a surgical procedure.

47. (Withdrawn) The method of claim 46, wherein the cardiovascular disease or condition is chosen from hypertension, arterial inflammation, rapid ventricular pacing, aortic bending, vascular heart disease, atrial fibrillation, congestive heart failure, sinus node dysfunction, angina, heart failure, atrial flutter, cardiomyopathy, coronary artery disease, coronary artery spasm, and arrhythmia.

48. (Withdrawn) The method of claim 46, wherein the subject is at risk of thrombosis due to immobilization due to medical or surgical illness.

49. (Withdrawn) The method of claim 46, wherein the surgical procedure is chosen from a vascular procedure, angioplasty, surgical revascularization, balloon

angioplasty, laser angioplasty, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, rotational atherectomy, stenting, and coronary artery stenting.

50. (Previously presented) The method of claim 45, wherein the soluble PSGL-1 protein is a human PSGL-1.

51. (Previously presented) The method of claim 45, wherein the soluble PSGL-1 protein or fragment thereof comprises an extracellular domain of human PSGL-1 protein.

52. (Previously presented) The method of claim 45, wherein the soluble PSGL-1 protein or fragment thereof comprises amino acid 42 to amino acid 60 of SEQ ID NO:2.

53. (Previously presented) The method of claim 45, wherein the soluble PSGL-1 protein or fragment thereof comprises amino acid 42 to amino acid 88 of SEQ ID NO:2.

54. (Previously presented) The method of claim 45, wherein the soluble PSGL-1 protein or fragment thereof comprises a non-PSGL-1 amino acid sequence.

55. (Previously presented) The method of claim 54, wherein the non-PSGL-1 amino acid sequence comprises an Fc portion of an immunoglobulin.

56. (Previously presented) The method of claim 55, wherein the soluble PSGL-1 protein or fragment comprises the amino acid sequence from amino acid 42 to amino acid 60 of SEQ ID NO:2.

57. (Previously presented) A method for treating, inhibiting, or preventing thrombosis in a subject at risk of thrombosis comprising identifying a human subject at risk of

thrombosis due to hypertension and administering to the subject a composition comprising an effective amount of a soluble PSGL-1 protein or fragment thereof having a P-selectin activity chosen from at least one of:

a) inhibiting P-selectin or E-selectin binding;

b) inhibiting adhesion of at least one of leukocytes to endothelial cells, leukocytes to platelets, leukocytes to blood vessels, and platelets to blood vessels;

c) inhibiting leukocyte recruitment to platelets and endothelial cells;

d) increasing leukocyte migration;

e) increasing movement of at least one of leukocytes and platelets relative to blood vessels; and

f) increasing leukocyte rolling velocity.

X. Evidence Appendix to Appeal Brief Under Rule 41.37(c)(1)(ix)

Appellants rely on the Declaration of Dr. Stefan Hemmerich, submitted on September 13, 2006, in support of these arguments. The Examiner entered this Declaration into the record on September 28, 2006, and a copy has been included with this filing. Additionally, Appellants rely on the following publications discussed in and attached to this Declaration:

- Cummings *et al.* U.S. Patent No. 5,464,778;
- THE MERCK MANUAL OF DIAGNOSIS AND THERAPY 1655 (17th ed. 1999);
- Larsen *et al.*, U.S. Patent No. 5,840,679;
- Lip *et al.*, "Hypertension and the prothrombotic state," J. Hum. Hyper. 14: 687-90 (2000);
- Blann *et al.*, "Evidence of platelet activation in hypertension," J. Hum. Hyper. 11:607-609 (1997);
- Araneo *et al.*, U.S. Patent No. 6,150,348;
- DeFrees *et al.*, U.S. Patent No. 5,604,207;
- Maugeri *et al.*, "Polymorphonuclear Leukocyte-Platelet Interaction: Role of P-selectin in Thromboxane B_2 and Leukotriene C_4 Cooperative Synthesis," *Thromb. Haem.* 72:450-456 (1994); and
- Johnston *et al.,* "Differential Roles of Selectins and the α4-Integrin in Acute, Subacute, and Chronic Leukocyte Recruitment In Vivo," *J. Immunol.* 159:4514-4523 (1997).

XI. Related Proceedings Appendix to Appeal Brief Under Rule 41.37(c)(1)(x)

Appellants are not aware of or relying on any decisions in related proceedings.